

REMARKS

Drawings

The Office Action objects to Figure 1 because it allegedly contains errors in the structure of cobalamin. In response, Applicants submit herewith a revised Figure 1 that addresses the concerns raised in the Office Action.

Claim Objections

The Office Action objects to claims 111 and 112 because they are multiple dependent claims and they depend from other multiple dependent claims. In response, Applicants have amended the multiple dependent claims from which claims 111 and 112 depend so that they only depend from one other claim.

Claim Rejections – 35 U.S.C. 112

The Office Action first rejects a number of claims because they do not include figure 1 within their text. In response, Applicants have amended the claims to include the reference figure.

The Office Action also rejects claim 18 for depending from non-elected claim 17. If claim 17 is found to be unpatentable after a search of all relevant species, Applicants will cancel claim 18 or amend it to depend from a properly allowable claim.

Claim Rejections – 35 U.S.C. 102

The Office Action rejects claims 1, 12-15, 18, 24, 49-51, 55, and 60, for allegedly being anticipated by Pinson et al. ("Synthesis of Two Doxorubicin-Cobalamin Bioconjugates," Ninth International Symposium on Recent Advances in Drug Delivery Systems, February 1999, pages 228-229). However, Pinson et al. discloses doxorubicin conjugated to the cobalt atom in vitamin B12. In contrast, the cobalt position in the present compounds is occupied by X which is defined as CN, OH, CH₃, or adenosyl in the claims. Thus, Pinson does not anticipate any of the pending claims.

Claim Rejections – 35 U.S.C. 103

The Office Action rejects claims 1, 3, 5, 7, 9, 12-1, 18, 20, 24, 49-51, 55-56, and 60-61 for allegedly being obvious over Smelter et al. ("Cytotoxicities of Tow New Cobalamin Bioconjugates," Ninth International Symposium on Recent Developments in Drug Delivery Systems, February 1999, pages 232-33) in view of Grissom et al. (WO 98/08859). Once again, both Smelter et al. and Grissom et al. disclose linkage of active moieties such as doxorubicin to vitamin B12 through the cobalt atom, while the present claims are limited to compounds in which the cobalt position is occupied by an X moiety, which is defined as CN, OH, CH₃, or adenosyl. Moreover, there is nothing in the references cited to suggest or motivate a skilled worker to link the doxorubicin through a position other than the cobalt atom. Therefore, it is respectfully submitted that the references do not support a *prima facie* case of obviousness.

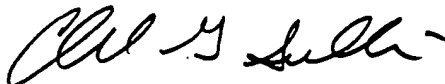
Double Patenting

The Office Action rejects a number of claims for obviousness-type double patenting over copending application no. 10/027,593. Upon an indication of allowable subject matter Applicants will file a suitable terminal disclaimer.

CONCLUSION

Applicants thank the Examiner for the attention he has thus far given to this application, and requests that he contact the undersigned or Sherry Knowles at 404-572-4600 should he have any questions concerning this response.

Respectfully submitted,



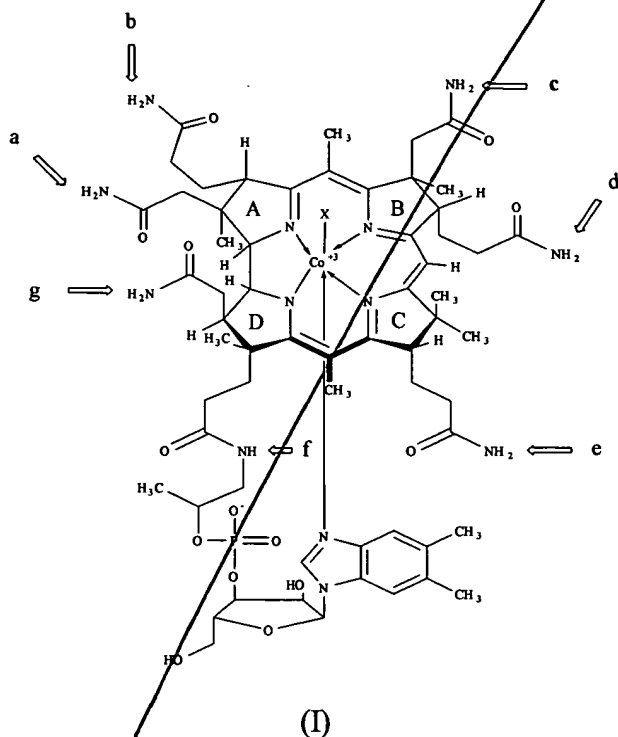
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K&S Docket: 07959.105025
3062618 v1

REPLACEMENT CLAIM SET

What is claimed is:

1. (Once Amended) A compound wherein a residue of a compound of formula I



is linked directly or by a linker to a residue of one or more chemotherapeutic agents; wherein X is CN, OH, CH₃, or adenosyl; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the b, d or e-carboxamide of the compound of formula I.
3. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-, d- or e-carboxamide of the compound of formula I.

4. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to the b-carboxamide of the compound of formula I.

5. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I.

6. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the d-carboxamide of the compound of formula I.

7. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

8. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the e-carboxamide of the compound of formula I.

9. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the e-carboxamide of the compound of formula I.

10. The compound of claim 1 wherein a residue of a first chemotherapeutic agent is linked directly or by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked directly or by a linker to a residue of the d-carboxamide of the compound of formula I.

11. The compound of claim 1 wherein a residue of a first chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

12. The compound of claim 1 wherein the chemotherapeutic agent is an antineoplastic agent.

13. The compound of claim 12 wherein the antineoplastic agent is a cytotoxic agent.

14. The compound of claim 13 wherein the cytotoxic agent is doxorubicin or paclitaxel.

a² 15. (Once Amended) The compound of claim 1 wherein at least one linker is of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-,

a2
cont'd
B1
-C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

16. The compound of claim 15 wherein W and Q are each -N(R)-.

a3
17. (Once Amended) The compound of claim 1 wherein at least one linker is of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

18. The compound of claim 17 wherein at least one of W and Q is -N(R)-.

19. The compound of claim 18 wherein n is in the range from about 2 to about 6, inclusive.

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B1
20. (Once Amended) The compound of claim 1 wherein the linker is a divalent radical formed from a peptide or an amino acid.

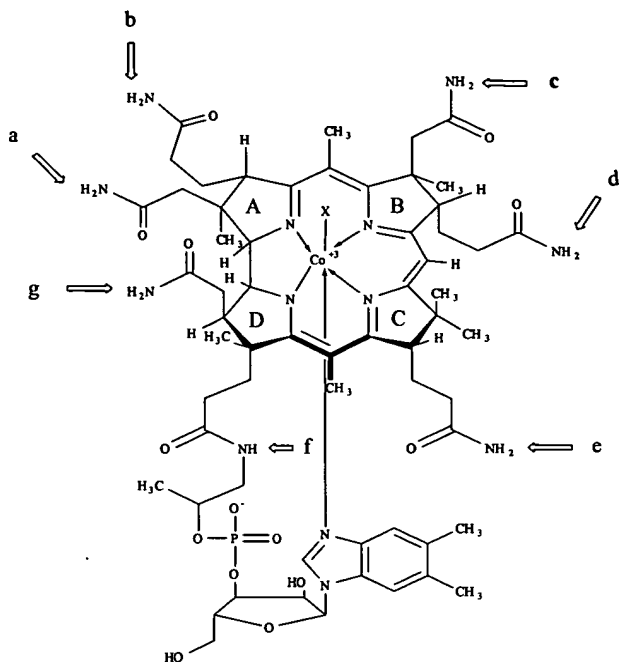
21. The compound of claim 20 wherein the peptide comprises 2 to about 25 amino acids.

22. The compound of claim 20 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

a5
23. (Once Amended) The compound of claim 1 wherein the linker is a 1,ω-divalent radical formed from a peptide.

24. (Once Amended) The compound of claim 1 wherein the linker separates the residue of a compound of formula I from the residue of the chemotherapeutic agent by about 5 angstroms to about 50 angstroms.

25. (Once Amended) A compound wherein a residue of a compound of formula I



(I)

is linked directly or by a linker to a residue of a chemotherapeutic agent through the 6-position and wherein a residue of the compound of formula I is linked directly or by a linker to a residue of one or more additional chemotherapeutic agents; or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the b-, d- or e-carboxamide of the compound of formula I.
27. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-, d- or e-carboxamide of the compound of formula I.
28. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to the b-carboxamide of the compound of formula I.
29. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I.

30. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the d-carboxamide of the compound of formula I.
31. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.
32. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the e-carboxamide of the compound of formula I.
33. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the e-carboxamide of the compound of formula I.
34. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked directly or by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked directly or by a linker to a residue of the d-carboxamide of the compound of formula I.
35. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

a⁶ 36. (Once Amended) The compound of claim 25 wherein at least one linker is of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

37. The compound of claim 36 wherein at least one of W and Q is -N(R)-.

a⁷ 38. (Once Amended) The compound of claim 25 wherein at least one linker is of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O), -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

39. The compound of claim 38 wherein at least one of W and Q is -N(R)-.

40. The compound of claim 38 wherein n is in the range of about 2 to about 6, inclusive.

a⁹
41. (Once Amended) The compound of claim 25 wherein a linker is a divalent radical formed from a peptide or an amino acid.

42. The compound of claim 41 wherein the peptide comprises 2 to about 25 amino acids.

43. The compound of claim 42 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

a⁹
44. (Once Amended) The compound of any one of claims 25 wherein the linker is a 1,ω-divalent radical formed from a peptide.

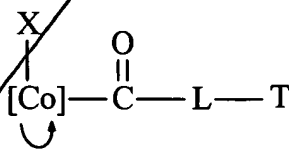
45. (Once Amended) The compound of any one of claims 25 wherein the linker separates the residue of a compound of formula I from the residue of the chemotherapeutic agent by about 5 angstroms to about 50 angstroms.

46. The compound of claim 25 wherein the chemotherapeutic agent is an antineoplastic agent.

47. The compound of claim 46 wherein the antineoplastic agent is a cytotoxic agent.

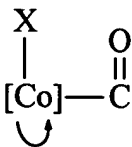
48. The compound of claim 47 wherein the cytotoxic agent is doxorubicin or paclitaxel.

a¹⁰
Sub B1
49. (Once Amended) A compound of formula II

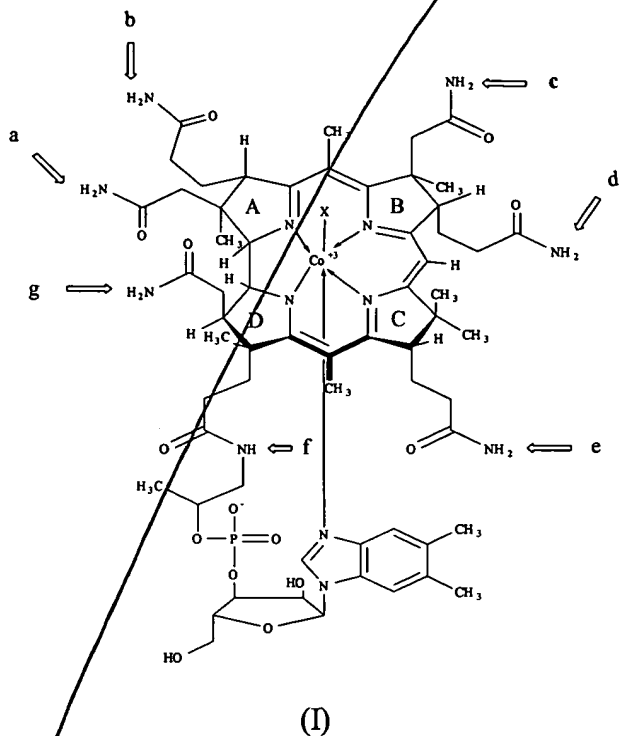


(II)

wherein



is a residue of the compound of formula I



X is CN, OH, CH₃, adenosyl, or LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

L is a linker or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

50. The compound of claim 49 wherein L and LL are each independently of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

51. The compound of claim 50 wherein at least one of W and Q is -N(R)-.

52. The compound of claim 49 wherein L and LL are each independently of the formula $W-(CH_2)_n-Q$ wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently $-N(R)C(=O)-$, $-C(=O)N(R)-$, $-OC(=O)-$, $-C(=O)O-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$, $-N(R)-$, or a direct bond; wherein each R is independently H or $(C_1-C_6)alkyl$.

53. The compound of claim 52 wherein at least one of W and Q is $-N(R)-$.

54. The compound of claim 52 wherein n is between about 2 and about 6.

Sub
BI 55. The compound of claim 49 wherein L separates T and the residue by about 5 angstroms to about 200 angstroms.

56. The compound of claim 49 wherein at least one of L and LL is a divalent radical formed from a peptide or an amino acid.

57. The compound of claim 56 wherein the peptide comprises 2 to about 25 amino acids.

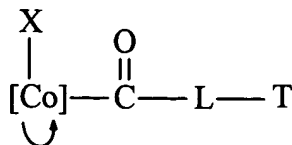
58. The compound of claim 56 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

59. The compound of claim 49 wherein at least one of L and LL is a $1,\omega$ -divalent radical formed from a peptide or an amino acid.

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BI 60. The compound of claim 49 wherein at least one of T and TT is a residue of paclitaxel or doxorubicin, or a pharmaceutically acceptable salt thereof.

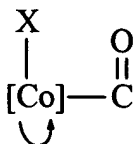
61. The compound of claim 49 wherein the $(C=O)$ in the group is attached to L-T at the b-, d- or e- position.

a" 62. (Once Amended) A compound of formula II



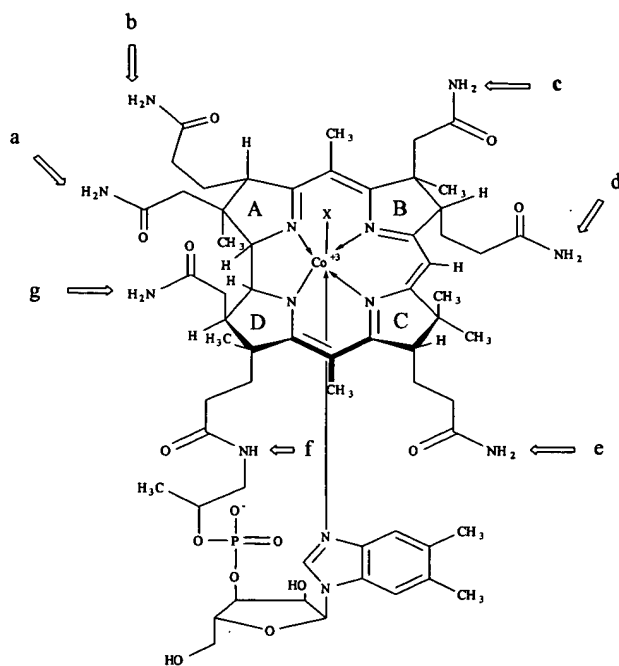
(II)

wherein



is a residue of the compound of formula I

*All
cont*



(I)

;

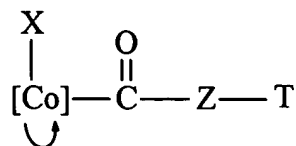
X is LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

L is a linker or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

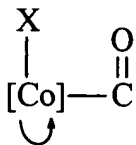
63. The compound of claim 62 wherein L and LL are each independently of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃₋₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.
64. The compound of claim 63 wherein at least one of W and Q is -N(R)-.
65. The compound of claim 62 wherein L and LL are each independently of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.
66. The compound of claim 65 wherein at least one of W and Q is -N(R)-.
67. The compound of claim 65 wherein n is between about 2 and about 6.
68. The compound of claim 62 wherein L separates T and the residue by about 5 angstroms to about 200 angstroms.
69. The compound of claim 62 wherein at least one of L and LL is a divalent radical formed from a peptide or an amino acid.
70. The compound of claim 69 wherein the peptide comprises 2 to about 25 amino acids.
71. The compound of claim 69 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.
72. The compound of claim 62 wherein at least one of L and LL is a 1,ω-divalent radical formed from a peptide.
73. The compound of claim 62 wherein at least one of T and TT is a residue of paclitaxel or doxorubicin, or a pharmaceutically acceptable salt thereof.
74. The compound of claim 62 wherein (C=O) in the group is attached to L-T is attached at the b-, d- or e- position.

a'2
75. (Once Amended) A compound of formula III:

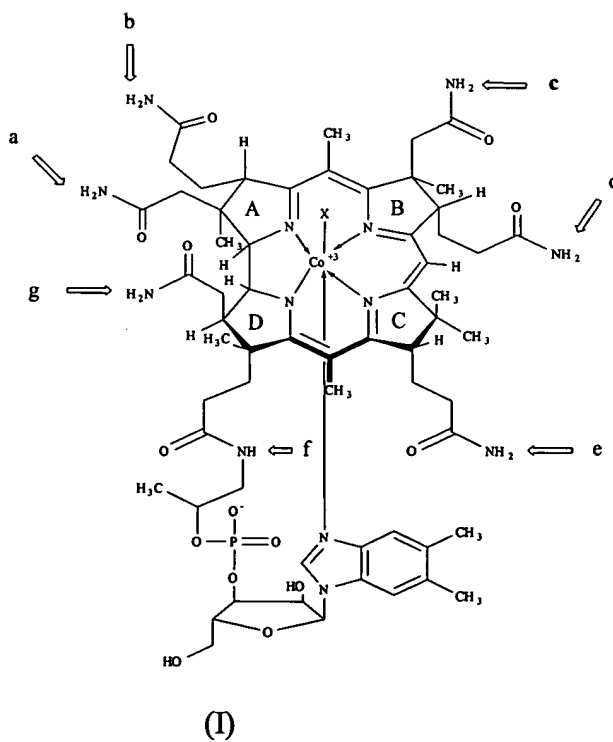


(III)

wherein



is a residue of a compound of formula I



A 12
Contd

X is CN, OH, CH₃, adenosyl, or ZZ-TT wherein ZZ is a linker or is absent and TT is a residue of a chemotherapeutic agent;

Z is -N(R)-, -O-, or -S-, wherein R is H or (C₁-C₆)alkyl or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

76. The compound of claim 75 wherein Z and ZZ are each independently of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

77. The compound of claim 76 wherein at least one of W and Q is -N(R)-.

78. The compound of claim 75 wherein Z and ZZ are each independently of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

79. The compound of claim 78 wherein at least one of W and Q is -N(R)-.

80. The compound of claim 78 wherein n is between about 2 and about 6.

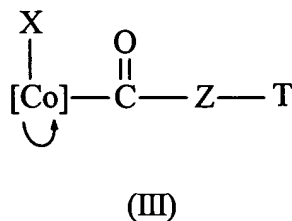
81. The compound of claim 75 wherein Z separates T and the residue by about 5 angstroms to about 200 angstroms.

82. The compound of claim 75 wherein at least one of Z and ZZ is a divalent radical formed from a peptide or an amino acid.

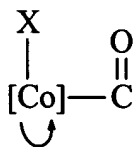
83. The compound of claim 82 wherein the peptide comprises 2 to about 25 amino acids.

84. The compound of claim 75 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

85. The compound of claim 75 wherein at least one of Z and ZZ is a 1,ω-divalent radical formed from a peptide.
86. The compound of claim 75 wherein the (C=O) in the group is attached to Z-T at the b-, d- or e- position.
87. The compound of claim 75 wherein at least one of T and TT is a residue of an antineoplastic agent.
88. The compound of claim 87 wherein the antineoplastic agent is a cytotoxic agent.
89. The compound of claim 88 wherein the cytotoxic agent is doxorubicin or paclitaxel.
90. (Once Amended) A compound of formula III:

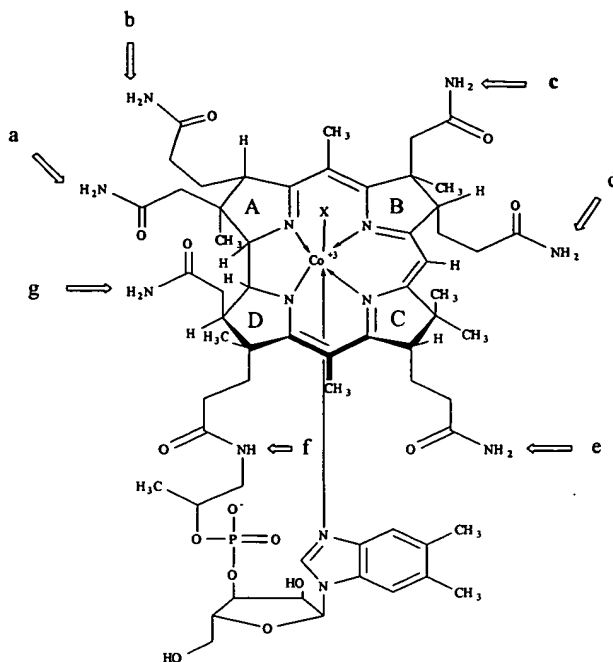


wherein



is a residue of the compound of formula I

A13
cont'd



(I)

X is LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

Z is -N(R)-, -O-, or -S-, wherein R is H, (C₁-C₆)alkyl, or absent; and

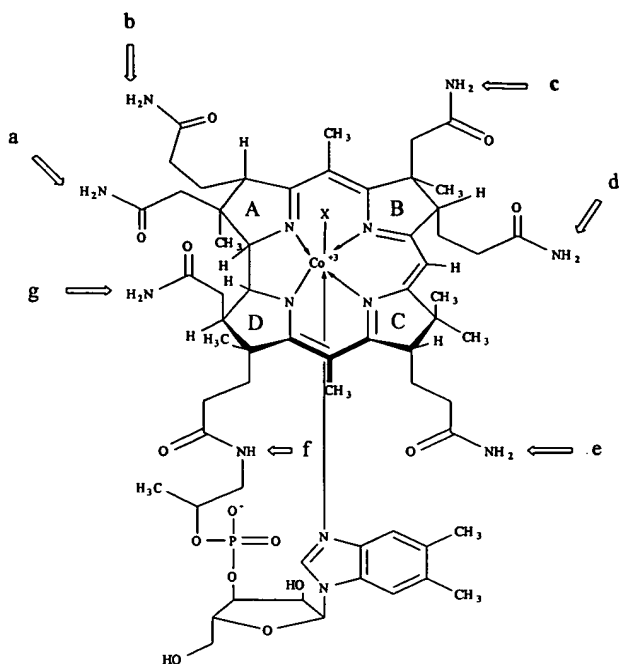
T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

91. The compound of claim 90 wherein Z and ZZ are each independently of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

92. The compound of claim 91 wherein at least one of W and Q is -N(R)-.

93. The compound of claim 90 wherein Z and ZZ are each independently of the formula $W-(CH_2)_n-Q$ wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently $-N(R)C(=O)-$, $-C(=O)N(R)-$, $-OC(=O)-$, $-C(=O)O-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$, $-N(R)-$, or a direct bond; wherein each R is independently H or $(C_1-C_6)alkyl$.
94. The compound of claim 93 wherein at least one of W and Q is $-N(R)-$ wherein each R is independently H or $(C_1-C_6)alkyl$.
95. The compound of claim 93 wherein n is between about 2 and about 6.
96. The compound of claim 90 wherein Z separates T and the residue by about 5 angstroms to about 200 angstroms.
97. The compound of claim 90 wherein at least one of Z and ZZ is a divalent radical formed from a peptide or an amino acid.
98. The compound of claim 97 wherein the peptide comprises 2 to about 25 amino acids.
99. The compound of claim 90 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.
100. The compound of claim 90 wherein at least one of Z and ZZ is a $1,\omega$ -divalent radical formed from a peptide.
101. The compound of claim 90 wherein $(C=O)$ in the group is attached to Z-T at the b-, d- or e- position.
102. The compound of claim 90 wherein at least one of T and TT is a residue of an antineoplastic agent.
103. The compound of claim 102 wherein the antineoplastic agent is a cytotoxic agent.
104. The compound of claim 103 wherein the cytotoxic agent is doxorubicin or paclitaxel.

105. A compound wherein a residue of a compound of formula I



(I)

is linked directly or by a linker to a residue of one or more chemotherapeutic agents; wherein X is CN, OH, CH₃, or adenosyl; wherein the compound of formula I is also linked directly or by a linker to a detectable radionuclide; or a pharmaceutically acceptable salt thereof.

106. The compound of claim 105 wherein the detectable radionuclide is linked to a residue of the b, d or e-carboxamide of the compound of formula I.

107. The compound of claim 105 wherein the detectable radionuclide is linked by a linker to a residue of the compound of formula I.

108. The compound of claim 105 wherein the detectable radionuclide is directly linked to a residue of the compound of formula I.

109. The compound of claim 105 wherein the detectable radionuclide is a non-metallic radionuclide.

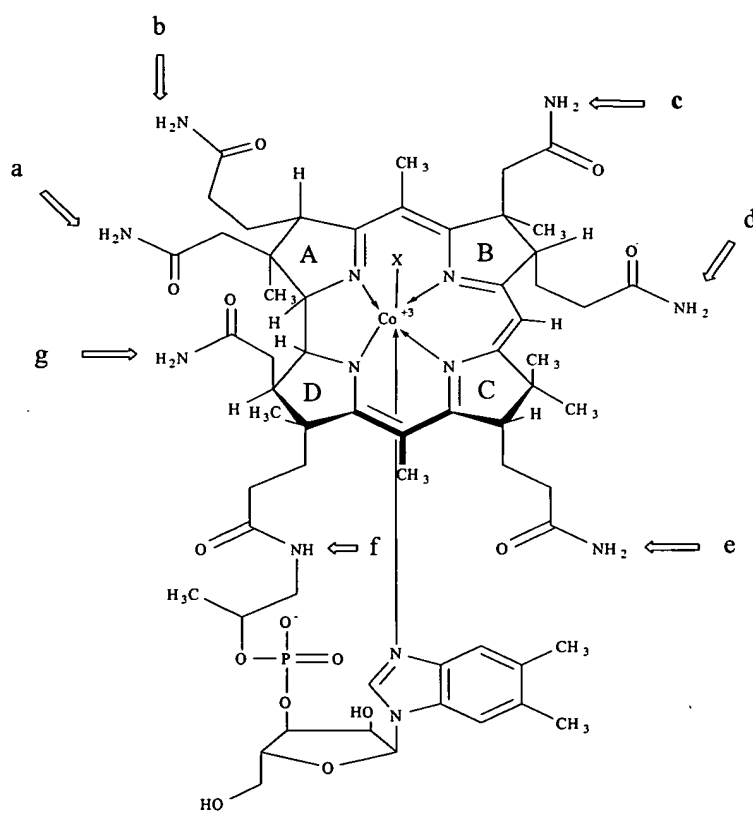
110. The compound of claim 109 wherein the non-metallic radionuclide is Carbon-11, Fluorine-18, Bromine-76, Iodine-123, or Iodine-124.
111. A pharmaceutical composition comprising a compound of any one of claims 1-110 and a pharmaceutically acceptable carrier.
112. A compound of any one of claims 1-110 for use in medical therapy or diagnosis.
113. The use of claim 105 for the manufacture of a medicament for imaging a tumor in a mammal.
114. The use of claim 113 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.
115. The use of a compound of any one of claims 1-110 for the manufacture of a medicament for treating a tumor in a mammal.
116. The use of claim 115 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.
117. A method of treating a tumor in a mammal in need of such treatment comprising administering to the mammal an effective amount of a compound of any one of claims 1-110.
118. The method of claim 117 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.
119. A method of imaging a tumor in a mammal in need of such imaging comprising administering to the mammal an effective amount of a compound of claim 105; and detecting the presence of the compound.

120. The method of claim 119 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.

VERSION OF CLAIMS TO SHOW CHANGES MADE

Claims 1, 15, 17, 20, 23, 24, 25, 36, 38, 41, 44, 45, 49, 62, 75, 90, and 105 are amended as follows:

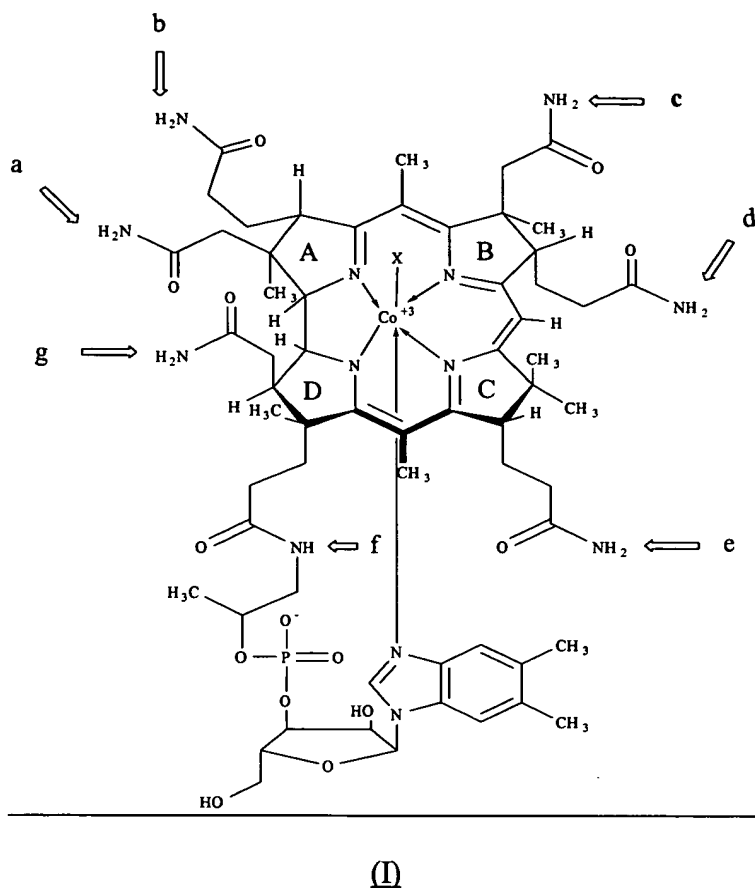
1. (Once Amended) A compound wherein a residue of a compound of formula I [(Figure I)]



is linked directly or by a linker to a residue of one or more chemotherapeutic agents; wherein X is CN, OH, CH₃, or adenosyl; or a pharmaceutically acceptable salt thereof.

15. (Once Amended) The compound of **[any one of]claim[s] 1[, 3, 5, 7, 9, 10, and 11]** wherein at least one linker is of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.
17. (Once Amended) The compound of **[any one of]claim[s] 1[, 3, 5, 7, 9, 10, and 11]** wherein at least one linker is of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.
20. (Once Amended) The compound of **[any one of]claim[s] 1[, 3, 5, 7, 9, 10, and 11]** wherein the linker is a divalent radical formed from a peptide or an amino acid.
23. (Once Amended) The compound of **[any one of]claim[s] 1[, 3, 5, 7, 9, 10, and 11]** wherein the linker is a 1,ω-divalent radical formed from a peptide.
24. (Once Amended) The compound of **[any one of]claim[s] 1[, 3, 5, 7, 9, 10, and 11]** wherein the linker separates the residue of a compound of formula I from the residue of the chemotherapeutic agent by about 5 angstroms to about 50 angstroms.

25. (Once Amended) A compound wherein a residue of a compound of formula I



is linked directly or by a linker to a residue of a chemotherapeutic agent through the 6-position and wherein a residue of the compound of formula I is linked directly or by a linker to a residue of one or more additional chemotherapeutic agents; or a pharmaceutically acceptable salt thereof.

36. (Once Amended) The compound of [any one of] claim[s] 25[, 27, 29, 31, 33, 34 and 35] wherein at least one linker is of the formula W-A-Q wherein A is $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_2\text{-C}_6)\text{alkenyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$, $(\text{C}_3\text{-C}_8)\text{cycloalkyl}$, or $(\text{C}_6\text{-C}_{10})\text{aryl}$, wherein W and Q are each independently $-\text{N}(\text{R})\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{N}(\text{R})-$, $-\text{OC}(=\text{O})-$, $-\text{C}(=\text{O})\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R})-$, $-\text{C}(=\text{O})-$, or a direct bond; wherein each R is independently H or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

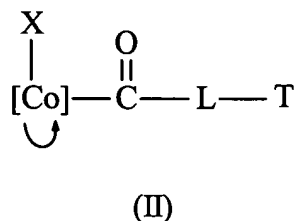
38. (Once Amended) The compound of [any one of] claim[s] 25[, 27, 29, 31, 33, 34 and 35] wherein at least one linker is of the formula $W-(CH_2)_n-Q$ wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently $-N(R)C(=O)-$, $-C(=O)N(R)-$, $-OC(=O)-$, $-C(=O)O-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$, $-N(R)-$, or a direct bond; wherein each R is independently H or (C_1-C_6) alkyl.

41. (Once Amended) The compound of [any one of] claim[s] 25[, 27, 29, 31, 33, 34 and 35] wherein a linker is a divalent radical formed from a peptide or an amino acid.

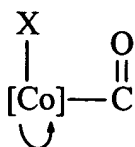
44. (Once Amended) The compound of [any one of] claim[s] 25[, 27, 29, 31, 33, 34 and 35] wherein the linker is a $1,\omega$ -divalent radical formed from a peptide.

45. (Once Amended) The compound of [any one of] claim[s] 25[, 27, 29, 31, 33, 34 and 35] wherein the linker separates the residue of a compound of formula I from the residue of the chemotherapeutic agent by about 5 angstroms to about 50 angstroms.

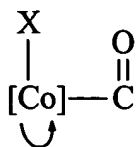
49. (Once Amended) A compound of formula II



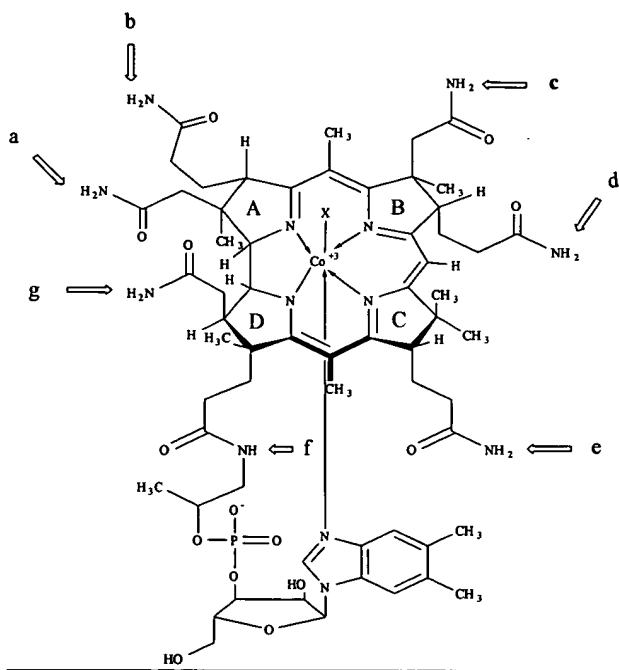
wherein



wherein



is a residue of the compound of formula I



(I)

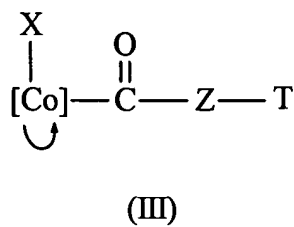
;

X is LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

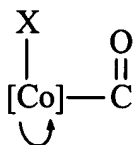
L is a linker or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

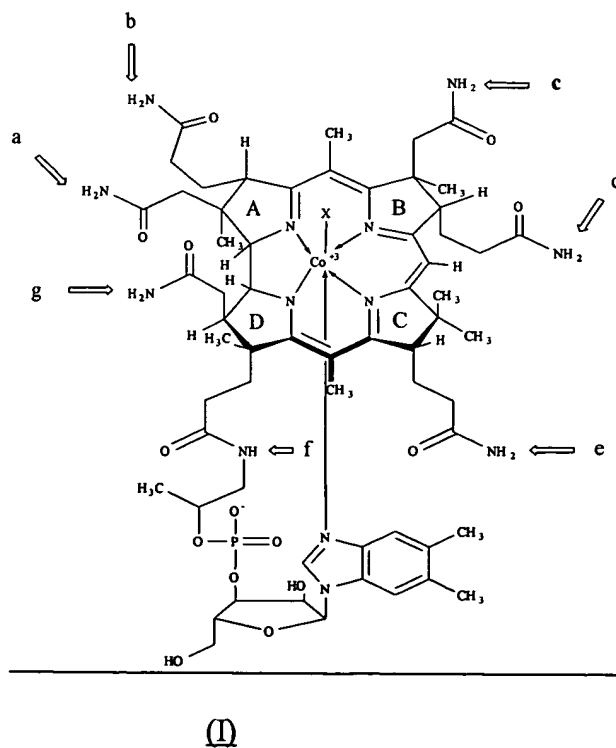
75. (Once Amended) A compound of formula III:



wherein



is a residue of a compound of formula I

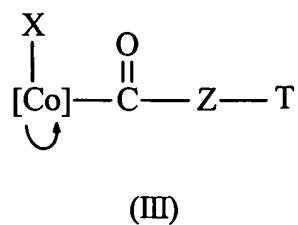


X is CN, OH, CH₃, adenosyl, or ZZ-TT wherein ZZ is a linker or is absent and TT is a residue of a chemotherapeutic agent;

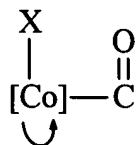
Z is -N(R)-, -O-, or -S-, wherein R is H or (C₁-C₆)alkyl or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

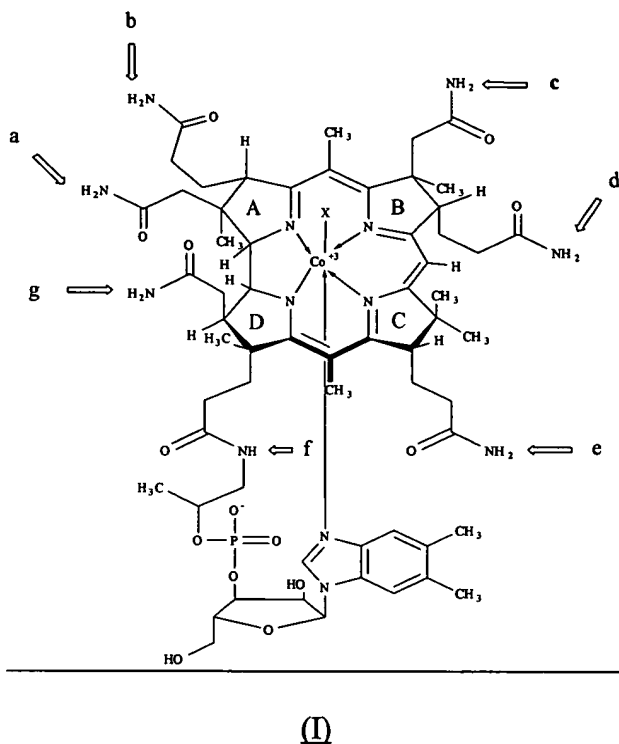
90. (Once Amended) A compound of formula III:



wherein



is a residue of the compound of formula I



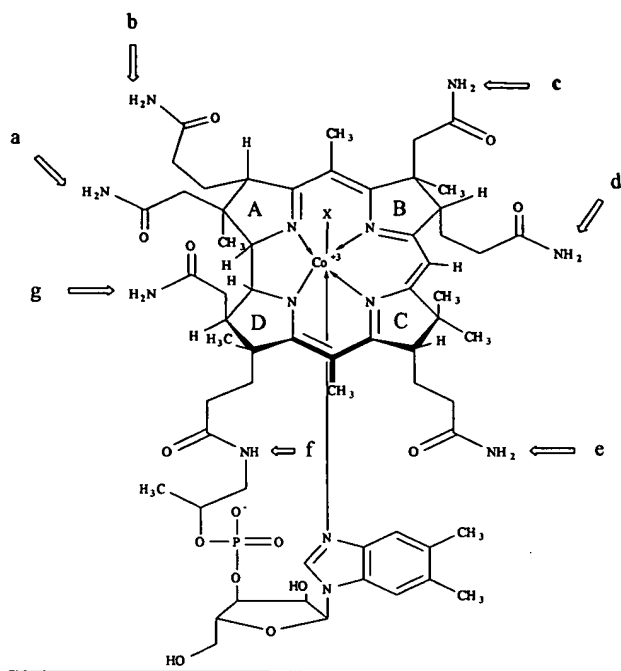
;

X is LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

Z is -N(R)-, -O-, or -S-, wherein R is H, (C₁-C₆)alkyl, or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

105. (Once Amended) A compound wherein a residue of a compound of formula I [(Figure 1)]



(I)

is linked directly or by a linker to a residue of one or more chemotherapeutic agents; wherein X is CN, OH, CH₃, or adenosyl; wherein the compound of formula I is also linked directly or by a linker to a detectable radionuclide; or a pharmaceutically acceptable salt thereof.

| | | |
|-----------|-----------|----------|
| APPROVED | O.G. FIG. | |
| BY | CLASS | SUBCLASS |
| DRAFTSMAN | | |

Serial No. 09/690,198
Amendment and Response to Office Action
December 3, 2002

REPLACEMENT FIGURE

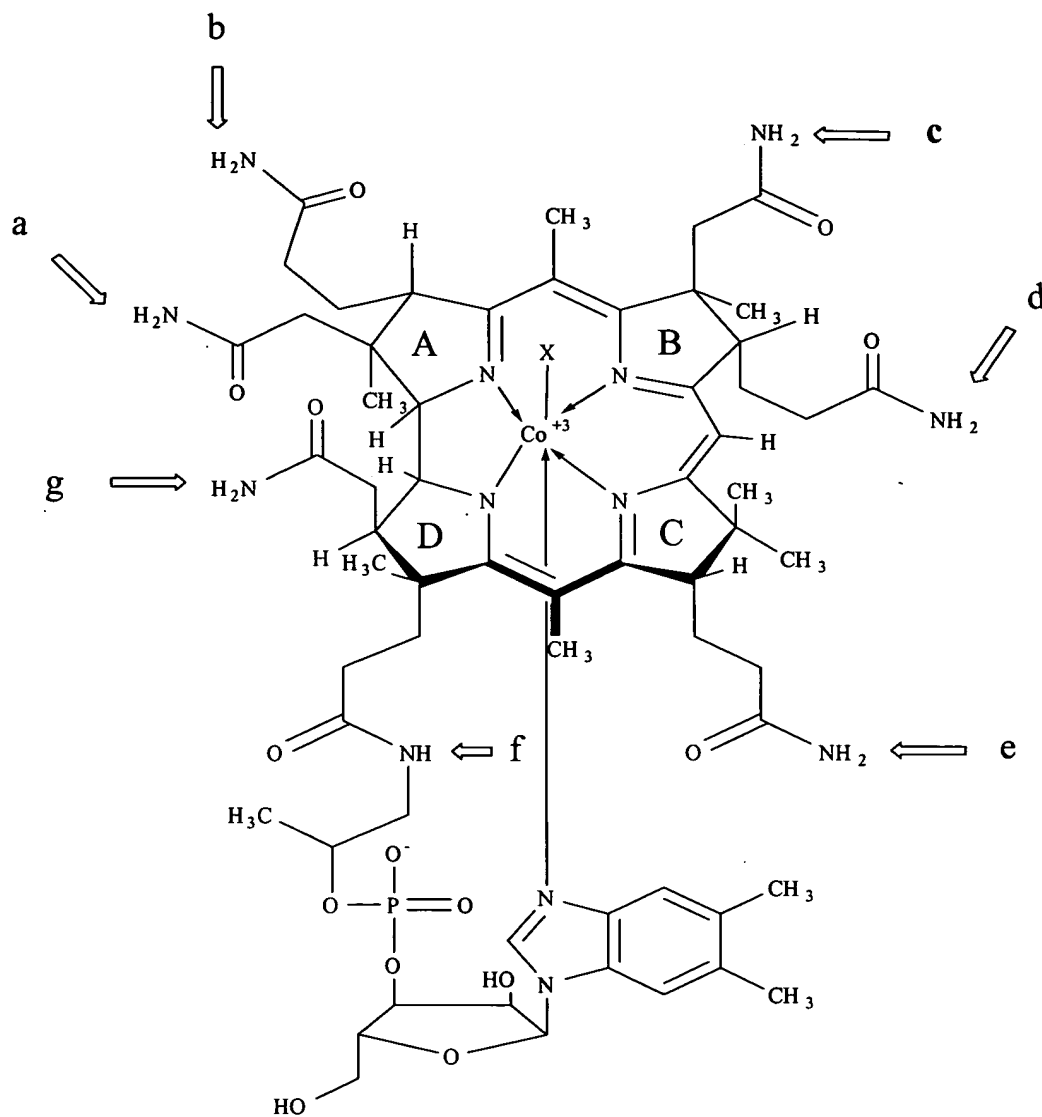


Figure 1